

Serial No.: 10/731,877
Conf. No.: 9392

- 6 -

Art Unit: 1651

REMARKS

Claims 26-39, 49-61, 70-85, 97, and 98 which were withdrawn from consideration, have now been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue claims similar or identical to these claims in one or more applications claiming priority to the instant application.

Independent claim 1 has been amended to incorporate the limitations of dependent claims 3 and 25. Independent claim 40 has been amended to incorporate the limitations of dependent claims 42 and 47. Independent claim 62 has been amended to incorporate the limitations of dependent claims 65 and 68. Dependent claims 6, 8, 87, and 91 have also been amended to provide proper antecedent basis. No new matter has been added.

Claims 3, 4, 10-16, 25, 41-43, 47, 48, 63-65, 68, 69, and 94-96 have been cancelled without prejudice or disclaimer.

Claims 1, 2, 5-9, 17-24, 40, 44-46, 62, 66, 67, and 86-93 are now pending for examination.

Rejections under 35 U.S.C. §102(b) in view of Marquisee

Claims 1, 6, and 7 have been rejected under 35 U.S.C. §102(b) as being anticipated by Marquisee, U.S. Patent No. 3,954,678 ("Marquisee").

Independent claim 1 has been amended to incorporate the limitations of dependent claims 3 and 25, neither of which were rejected in view of Marquisee. Accordingly, it is believed that claim 1, as amended, is novel in view of Marquisee, and it is therefore respectfully requested that the rejection of claims 1, 6 and 7 be withdrawn.

Rejections under 35 U.S.C. §103(a) in view of Chang, Setala, Yamamoto, Shigyo, and the Online Medical Dictionary

Claims 1-4, 6-8, 10-17, 25, 40-45, 47, 48, 62-66, 68, 69, 86-91, and 93-96 have been rejected under 35 U.S.C. §103(a) as being unpatentable over of Chang, *et al.*, U.S. Patent No. 6,217,859 ("Chang"), in view of Setala, U.S. Patent No. 4,022,883 ("Setala"), and in further view of Yamamoto, *et al.*, U.S. Patent No. 5,627,065 ("Yamamoto"), and Shigyo, *et al.*, U.S. Patent No. 5,728,562 ("Shigyo") and in light of the Online Medical Dictionary (<http://cancerweb.ncl.ac.uk/cgi-bin/omd>, accessed 2/28/05).

Serial No.: 10/731,877
Conf. No.: 9392

- 7 -

Art Unit: 1651

Claims 1 and 86

With respect to independent claims 1 and 86, the combination of cited references does not teach all of the elements of the claimed invention. It is not seen where in Chang or Setala is there a disclosure or a suggestion of an isolated enzyme. However, it was suggested in the Office Action that the motivation to use isolated enzymes instead of the genetically engineered cells described by Chang comes from the knowledge in the art concerning the desirability of using isolated enzymes versus modified cells and the interchangeability (functional equivalents) of isolated enzymes and genetically modified cells.¹

Initially, Applicants disagree that an isolated enzyme is the functional equivalent of an enzyme expressed internally by a cell. Enzymes expressed internally within a cell are in a substantially different environment than enzymes exposed to the digestive system, for example, in terms of pH, chemical reactants, other enzymes within the digestive system, etc. The enzymes are not released from the cells, but rather, function intracellularly. For instance, many enzymes are known to be very labile at low pH's. Thus, one of ordinary skill in the art would not believe that an enzyme naturally expressed internally within a cell to be the functional equivalent of an isolated enzyme exposed to the environment of the digestive system.

Moreover, it was not known, at the time the instant invention was made, whether both uric acid and creatinine were present in the digestive system at concentrations which would have made their removal therapeutically useful, and thus, one of ordinary skill in the art would not have been motivated to use at least two different types of isolated uremic enzymes, such as isolated uricase and isolated creatininase, in an oral delivery composition.

Applicants also disagree that one of skill in the art would have substituted or would have had a reasonable expectation of success in substituting the genetically transformed cells of

¹ For instance, the Patent Office states on page 7, second paragraph, that: "One of ordinary skill in the art would have been motivated to encapsulate isolated enzymes, instead of whole cells, because isolated enzymes can be easily purchased from commercial sources, are less complicated in terms of biocompatibility, immune reactions and overall safety than genetically modified organisms, isolated enzymes require less effort in storage, packaging and transportation, and compositions comprising isolated enzymes are easier to get approved by the FDA than genetically modified organisms. One would have expected isolated uremic enzymes to successfully breaking down uremic toxins as well as uremic enzymes secreted from transgenic microorganisms because isolated uremic enzymes and secreted uremic enzymes are functional equivalents. Thus, simply because Chang et al. and Setala do not specifically teach using isolated enzymes, they do not teach or suggest negative results when isolated enzymes are used."

Serial No.: 10/731,877
Conf. No.: 9392

- 8 -

Art Unit: 1651

Chang with isolated enzyme. Chang specifically teaches in the Background of the Invention that "Several attempts, including use of oral feeding of oxystarch and urease zirconium phosphate have been applied to remove these unwanted metabolites from the body fluid compartments without success. The amounts of oxystarch and urease-zirconium-phosphate needed were too large to allow for use in the routine treatment of the patients." Further, Chang includes Figure 10 and its accompanying discussion (Col. 3, lines 18-20 and Col. 9, lines 40-55), which relate to a comparison of oral administration of encapsulated genetically altered bacteria versus enzymes. Chang concludes his discussion with the statement that "the required dosages for oxystarch and microencapsulated urease-zirconium phosphate are too large too allow them for routine daily use in patients (Col. 9, lines 50-52)." Thus, one of ordinary skill in the art reading Chang would not have been motivated to substitute isolated enzymes for genetically altered cells simply because they are commercially or readily available. One of ordinary skill in the art would also not have assumed that isolated enzymes and genetically altered cells are functionally equivalent.

Respectfully, the burden is on the Patent Office to show that the prior art teaches, suggests, or motivates the inventions as claimed, and the Patent Office has not satisfied this burden. Absent any evidence of any teaching, suggestion, or motivation anywhere in the prior art, or within the knowledge of one of ordinary skill as of at least the filing date of the invention, the Patent Office's rejection would appear to be a rejection based solely on hindsight or speculation, which is improper.

Accordingly, it is believed that claims 1 and 86 are patentable over Chang, Setala, Yamamoto, Shigyo, and the Online Medical Dictionary, and it respectfully requested that the rejection of these claims be withdrawn. Claims 2, 5-9, 17-24, and 87-93 each depend, directly or indirectly, from independent claims 1 and 86, and are believed to be allowable for at least the above-described reasons. Withdrawal of the rejections of these is therefore respectfully requested. (The other claims depending from claims 1 and 86 have been cancelled, rendering their rejection moot.)

Claims 40 and 62

Regarding independent claims 40 and 62, it is not seen where in either Chang or Setala is there a disclosure or a suggestion of transfecting a cell with a uricase gene or a creatininase gene.

Serial No.: 10/731,877
Conf. No.: 9392

- 9 -

Art Unit: 1651

The Patent Office notes that motivation to make the combination of Chang and Setala can be found in Setala, Col. 3, lines 18-36, which states:

Besides the degradation of urea, different microorganisms, because of the enzyme system contained therein, are capable of degrading creatine, creatinine, uric acid and so on, that is, those NPN compounds which accumulate in the organism of uremic patients. The formation of some of the enzyme systems in the organism depends on the presence of the substrate in the medium. The enzymes responsible for the oxidation of creatinine, lactose or malonic acid, are "totally adaptive", i.e. they are not formed in the absence of the substrate in question. The enzymes responsible for the degradation of several other substances, as for example uric acid, amino acids, lactic acid are "partly adaptive", i.e. their formation occurs to a certain degree in the absence of the substrate from the medium and is highly increased by its addition to the medium. Other enzyme systems, as, for example, those responsible for the oxidation of glucose or glycerol are constitutive.

Although this passage, and Setala in general, describes microorganisms capable of degrading creatine, creatinine, and uric acid, it is not seen how this would lead one of ordinary skill in the art to combine Setala with Chang in the manner stated in the Office Action. This passage does not appear to teach or suggest that a microorganism transfected with additional creatine, creatinine, or uric acid genes is desirable. In fact, this passage appears to teach away from this concept, as this passage implies that microorganisms (i.e., soil microorganisms) capable of degrading creatine, creatinine, and uric acid are readily obtainable, and thus, there would be no motivation for one of ordinary skill in the art to transfect such a microorganism in order to give the microorganism the ability to degrade creatine, creatinine, or uric acid. Accordingly, there appears to be no motivation to combine Setala with Chang, as suggested by the Office Action.

As described above, it is respectfully submitted that the Patent Office must initially come forward with some evidence showing a teaching, suggestion, or motivation in the prior art, or within the knowledge of one of ordinary skill in the art as of the filing date of the invention, that the invention as claimed is obvious in order to provide a *prima facie* case of obviousness. Absent any actual evidence to support its conclusions, the Patent Office's rejection would appear to be a rejection based solely on hindsight or speculation, which is improper.

Even if one of skill in the art were motivated to make the combination suggested by the Patent Office, one would not have a reasonable expectation of success. Claims 40 and 62 include the limitations of former claims 42 and 65, respectively, that require one cell expressing

Serial No.: 10/731,877
Conf. No.: 9392

- 10 -

Art Unit: 1651

uricase and creatininase, or urease, uricase and creatininase, respectively. One of skill in the art would not have had a reasonable expectation of success in combining two or three of the genes in a single cell since, as previously described, it was not known at the time the instant invention was made whether uric acid and creatinine were each present in the intestine at concentrations which would make their removal therapeutically useful. Thus, there would have been no motivation to one of ordinary skill in the art to transfect a cell with at least a uricase gene and a creatininase gene for use in an oral delivery composition, nor would that person of ordinary skill have had a reasonable expectation of success that such a composition would have been effective in treating a subject.

Accordingly, it is believed that independent claims 40 and 62 are patentable over Chang, Setala, Yamamoto, Shigyo, and the Online Medical Dictionary, and it respectfully requested that the rejection of these claims be withdrawn. Claims 44-46, 66, and 67 each depend, directly or indirectly, from independent claims 40 and 62, and are believed to be allowable for at least the above-described reasons. Withdrawal of the rejections of these claims is also respectfully requested. (The other claims depending from claims 40 and 62 have been cancelled, rendering their rejection moot.)

Rejections under 35 U.S.C. §103(a) in view of Chang, Setala, Yamamoto,
Shigyo, the Online Medical Dictionary, and Merriam-Webster

Claims 5 and 9 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chang in view of Setala, further in view of Yamamoto and Shigyo, and still further in light of the Medical Dictionary, and the Merriam-Webster Online Dictionary (<http://www.m-w.com>, access date not given) ("Merriam-Webster").

Applicants do not concede to the accuracy of Merriam-Webster, especially from the viewpoint of one of ordinary skill in the art. Moreover, for at least the reasons explained above with respect to the rejection under §103(a) in view of Chang, Setala, Yamamoto, Shigyo, and the Online Medical Dictionary, it is believed that claim 1 is not unpatentable over any combination of these references. Accordingly, there is no suggestion or motivation in any of Chang, Setala, Yamamoto, Shigyo, the Online Medical Dictionary, and Merriam-Webster to substitute isolated enzymes for genetically altered cells or to make the modification (e.g., with respect to acid

Serial No.: 10/731,877
Conf. No.: 9392

- 11 -

Art Unit: 1651

degradation and/or enteric coating) suggested in the Office Action. Thus, withdrawal of the rejection of claims 5 and 9 is respectfully requested.

Rejections under 35 U.S.C. §103(a), in view of Chang, Setala, Yamamoto,
Shigyo, Sparks, Wolfe, and the Online Medical Dictionary

Claims 18-21, 46, 67, and 92, have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chang in view of Setala, further in view of Yamamoto and Shigyo, and still further in view of Sparks, *et al.*, "Binders to remove uremic waste metabolites from the GI tract," *Trans. Amer. Soc. Artif. Int. Organs*, 18:458-464, 484, 1972 ("Sparks") and Wolfe, and in light of the Online Medical Dictionary.

These claims depend, directly or indirectly, from independent claims 1, 40, 62, and 86. For at least the above-described reasons with respect to the rejection under §103(a) in view of Chang, Setala, Yamamoto, Shigyo, and the Online Medical Dictionary, Applicants believe that claims 1, 40, 62, and 86 are not unpatentable over any combination of these references. Accordingly, there is no suggestion or motivation to combine Chang, Setala, Yamamoto, Shigyo, the Online Medical Dictionary, Sparks, and Wolfe in the manner suggested by the Patent Office. Thus, it is respectfully requested that the rejection of claims 18-21, 46, 67, and 92 be withdrawn.

Rejections under 35 U.S.C. §103(a) in view of Chang, Setala,
Yamamoto, Shigyo, Smith, and the Online Medical Dictionary

Claims 22-24, 46, 67, and 92 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chang in view of Setala, further in view of Yamamoto and Shigyo, and still further in view of Smith, *et al.*, U.S. Patent No. 4,857,555 ("Smith") and in light of the Online Medical Dictionary.

Claims 22-24, 46, 67, and 92 depend, either directly or indirectly, from independent claims 1, 40, 62, and 86. For at least the above reasons with respect to the rejection under §103(a) in view of Chang, Setala, Yamamoto, Shigyo, and the Online Medical Dictionary, it is believed that claims 1, 40, 62, and 86 are not unpatentable over any combination of these references. Accordingly, there is no suggestion or motivation to combine Chang, Setala, Yamamoto, Shigyo, Smith, and the Online Medical Dictionary as suggested by the Patent Office. Thus, withdrawal of the rejection of claims 22-24, 46, 67, and 92 is respectfully requested.

Serial No.: 10/731,877
Conf. No.: 9392

- 12 -

Art Unit: 1651

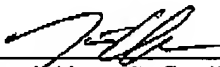
CONCLUSION

In view of the foregoing, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this response, that the application is not in condition for allowance, the Examiner is requested to call the undersigned at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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